# 1. The Clinical Trial Process

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# The Clinical Trial Process

### Learning Objectives

- Identify the steps in the drug development process
- Name the various types and phases of clinical trials

## The Drug Development and Approval Process

Clinical trials are a key part of the drug development and approval process. The entire process takes place under the watchful eye of the Food and Drug Administration (FDA). As a consumer protection agency of the U.S. Department of Health and Human Services, FDA is required by law to review all test results for new drugs to ensure that they are safe and effective for specific uses. "Safe" does not mean that the product is free of possible adverse side effects; rather, it means that its potential benefits outweigh any known risks. The FDA approval process is focused on drugs, but similar processes exist for the approval of:

- New devices (e.g., infusion pumps)
- Agents (e.g., vitamins and medications)
- Biologics (e.g., vaccines)

For purposes of illustration, the process outlined in this text focuses on drug approval.

Before a new drug or biologic agent that shows promising results in the lab can be tested in people, its sponsor must submit an Investigational New Drug (IND) application to FDA. Once the application is approved, the sponsor can begin testing the drug in clinical trials with human participants. If these trials demonstrate that the new drug is safe and superior to standard treatment, the sponsor can file a New Drug Application (NDA) or a Biologics

## Steps in the Drug Development Process

1. **Early research and preclinical testing.** During early research and preclinical testing, drugs undergo basic laboratory investigation and animal model testing for efficacy and toxicity. This step takes about 4 years.
2. **Investigational New Drug application.** The trial sponsor files an Investigational New Drug (IND) application with FDA. If FDA approves the application, clinical trials begin.
3. **Phase 1 clinical trial.** Phase 1 trials determine the safety and appropriate dosage of the drug for humans. It might take about 2 years before enough participants enroll in the trial. If phase 1 trials are successful, researchers design phase 2 trials.
4. **Phase 2 clinical trial.** Phase 2 trials evaluate the effectiveness of the drug and look for side effects. It might take up to 2 years to enroll participants for these trials. If phase 2 trials are successful, researchers design phase 3 trials.
5. **Phase 3 clinical trial.** Phase 3 trials evaluate the effectiveness of the new treatment, compared to standard treatment. It might take 3 to 4 years to enroll enough participants for these trials. Researchers report trial results in peer-reviewed scientific journals and at professional meetings.
6. **New Drug Application.** The trial sponsor files an NDA or BLA with FDA. The sponsor submits this application to FDA once it has adequate data to support a certain indication for a drug (usually by finding that the drug is safe and superior to standard treatment in a definitive phase 3 trial).
7. **FDA approval.** FDA approves the claim that is being made about the drug, which takes up to about 1½ years. After approval, it can be marketed to the public. FDA approval allows the drug to be "labeled" for a specific use. This label includes information on the drug's dosage, indications, safety, and side effects.

License Application (BLA) to FDA. Only after FDA approves the drug can it be marketed.

For an overview of the drug approval process from start to finish, see FDA's *From Test Tube to Patient*. This book tells the story of new drug development in the United States and highlights the consumer protection role of FDA. Call 1-888-INFO-FDA or see the Web site *www.fda.gov/cder/about/whatwedo/testtube.pdf*.

## Types and Phases of Clinical Trials

Cancer clinical trials focus on developing new strategies for the prevention, detection, treatment, and overall improvement of the care and quality of life of people with cancer or people at high risk for developing cancer. In cancer research, a clinical trial is designed to show how a particular anticancer strategy affects the people who receive it.

Clinical trials differ by type and phase, but they all involve rigorous scientific testing. Each type of clinical trial attempts to answer different research questions:

- **Prevention trials:** What kinds of interventions—such as lifestyle modifications, dietary supplements, or drugs—can prevent cancer from occurring?
- **Screening and early detection trials:** What tests can find cancer as early as possible in healthy people?
- **Diagnostic trials:** How can new tests or procedures identify a suspected cancer earlier or more accurately?
- **Genetics trials:** Can gene-transfer therapy be used to treat cancer?
- **Treatment trials:** What new interventions (e.g., drugs, biologics, surgical procedures, radiation) can help people who have cancer?
- **Quality-of-life and supportive care trials:** What kinds of interventions can improve the comfort and quality of life of people who have cancer?

Clinical trials occur in four phases, each of which is designed to answer different research questions:

- **Phase 1:** How does the treatment affect the human body? How should the treatment be given? What dosage is safe?
- **Phase 2:** Does the treatment do what it is supposed to do for a particular cancer? How does the treatment affect the human body?
- **Phase 3:** Is the new treatment (or new use of a treatment) better than current practice?
- **Phase 4:** What are the effects of an approved treatment?

The phases of clinical trials are explained in the context of drug treatment trials on the pages that follow. But the same concepts apply to most types of clinical trials, which are described after treatment trials.

| | Phase 1 | Phase 2 | Phase 3 | Phase 4 |
|---|---|---|---|---|
| **Number of participants** | 15-30 people | Less than 100 people | Generally, from 100 to thousands of people | Several hundred to several thousand people |
| **Purpose** | • To find a safe dosage<br>• To decide how the agent should be given<br>• To observe how the agent affects the human body | • To determine if the agent or intervention has an effect on a particular cancer<br>• To see how the agent or intervention affects the human body | • To compare the new agent or intervention (or new use of a treatment) with the current standard | • To further evaluate the long-term safety and effectiveness of a new treatment |

## Treatment Trials

Treatment trials are designed to test the safety and effectiveness of new drugs, biological agents, techniques, or other interventions in people who have been diagnosed with cancer. These trials evaluate the potential clinical usefulness of a therapy or compare an investigational treatment against standard treatment, if there is one.

### Phase 1

Phase 1 trials are the first step in transforming laboratory data into clinical care. While the primary goal of a phase 1 trial is to determine the toxic effects, pharmacological behavior, and recommended dosage of a therapy or technique for future trials, these trials are conducted with therapeutic intent.

In a phase 1 trial, the study participants (usually less than 30 people) are divided into cohorts of three to six participants. Each cohort of participants is treated with an increased dose of the new therapy or technique. Results in early participants greatly influence the dose subsequent participants receive. Initial dosage is based on preclinical testing and is usually quite conservative. If no serious side effects are seen in the initial group after a period of time, usually 3 to 4 weeks, the next group of participants receives a higher dose. This pattern is repeated until a certain percentage of participants experience dose-limiting toxicity—that is, side effects strong enough that the next group of participants should not get a higher dose. The highest dose with acceptable toxicity is determined to be appropriate for further testing.

Phase 1 trials are not limited to "first in human" studies. Subsequent phase 1 trials often evaluate new schedules or combinations of established drugs or radiation. Later phase 1 trials may also be conducted to evaluate toxicity, response, and pharmacokinetics in populations that might not have been included in prior trials, such as children or the elderly. Some phase 1 trials are pilot trials for larger trials designed to determine the interaction of a drug with another treatment or substance.

*Who Participates*

Almost all phase 1 trials of new anticancer drugs involve participants with a cancer that lacks or does not respond to standard treatment. People with many types of cancer can participate in the same phase 1 trial. Participants are generally required to have organ function capable of metabolizing and excreting the drug and a 1- to 2-month life expectancy, in order to evaluate the drug's effects and the body's response to it.

*Possible Benefits*

- If the new agent under study has an effect on the cancer, participants may be among the first to benefit.

*Possible Risks*

- Because phase 1 trials are often the first studies involving humans, unpredictable side effects can occur.

**Phase 2**

Phase 2 trials are designed to evaluate the effectiveness of the drug in a somewhat larger group of participants (usually under 100), using the dosage determined to be safe in phase 1 trials. On the basis of their findings in phase 1 trials, researchers often focus phase 2 trials on cancers for which no effective treatment exists and/or that are most likely to show a response to therapy. In choosing which type of cancer to study, researchers may also take into account effective alternatives and choose a cancer that has none. Some anticancer compounds being developed target molecular pathways in specific cancers, a development that may affect the cancers chosen for phase 2 trials.

In most phase 2 trials, all participants receive the same dose of the drug (or undergo the same intervention). The new treatment is assessed for effectiveness, and additional safety information is noted. Even if the new treatment seems effective, it usually requires further testing before entering widespread use. Because the treatment has not been compared to any other therapy or technique, its relative value is unclear, and it is impossible to rule out other factors that may have influenced its effectiveness. In addition, phase 2 trials are often too short to determine long-term benefits; larger and longer phase 3 trials are more suited to this purpose.

Some phase 2 trials compare different schedules of administering the same drug. At the end of such trials, the most promising regimen is chosen to move into phase 3 trials. Participants in this type of phase 2 trial are assigned at random to either the investigational group, which is given the new treatment, or the control group, which receives the standard treatment. Neither the participants nor their doctors choose which group individual participants will be in.

*Who Participates*

Generally, people who take part in phase 2 trials have not found the current standard of care effective or have cancers for which there is no standard treatment. Participants are generally required to have adequate organ function, a 3-month life expectancy, and a limited number of prior treatments.

*Possible Benefits*

- If the new agent has an effect on the cancer, participants may be among the first to benefit.

*Possible Risks*

- Unpredictable side effects may occur.

**Phase 3**

Phase 3 trials are large trials (usually involving more than 100 participants) designed to determine whether a new therapy or technique is more effective or less debilitating than a standard treatment. These trials are conducted at multiple institutions around the country, including community settings. Because the results of phase 3 trials guide health care professionals and people with cancer in making treatment decisions, their results should apply to aspects such as survival time and quality of life.

Like phase 2 trials, phase 3 trials usually focus on specific types of cancer. Participants enrolling in a phase 3 trial are assigned at random to an investigational group, which is given the new treatment, or a control group, which receives the current standard treatment. Some trials can also include more than two study groups, depending on the research questions being asked.

*Who Participates*

Many people with cancer get their first treatment in a phase 3 trial. Eligibility requirements vary with the disease stage or other factors being studied. Phase 3 trials typically involve large numbers of participants in order to determine true effectiveness.

*Possible Benefits*

- Regardless of the group a participant is assigned to, he or she will receive at a minimum the best widely accepted standard treatment.
- If a participant is taking the new treatment and it is shown to work, he or she may be among the first to benefit.

*Possible Risks*

- New treatments under study are not always better than, or even as good as, standard treatment.
- New treatments may have side effects that are worse than those of standard treatment.
- Despite phase 1 and 2 testing, unexpected side effects may occur.
- If the new treatment has benefits, it still may not work for every participant (just as standard treatments do not help everyone).
- Participants receiving the standard treatment may not benefit as much as those receiving the new one.

## Finding Out About Standard Cancer Care

The National Cancer Institute's Web site *www.cancer.gov* contains a database of the latest information about cancer and clinical trials. Specialists review current literature from more than 70 medical journals, evaluate its relevance, and synthesize it into clear summaries for the public and health professionals. Many of the summaries are also available in Spanish.

### Phase 4

Phase 4 trials are used to further evaluate the long-term safety and effectiveness of a treatment. Less common than phase 1, 2, and 3 trials, phase 4 trials usually take place after the new treatment has been approved for standard use.

## Other Types of Trials

### Adjuvant and Neoadjuvant Treatment Trials

Adjuvant trials are additional therapy after standard treatment. They are designed to prevent the recurrence of cancer in people who no longer show clinical evidence of disease. Adjuvant trials attempt to treat the subclinical or microscopic disease thought to be responsible for cancer recurrence and therefore improve disease-free and overall survival. The combination of standard and adjuvant treatments is initially tested in a small feasibility or pilot study similar to a single-agent phase 2 trial. This is followed by a randomized phase 3 trial if the combination proves safe and effective.

Neoadjuvant trials are additional therapy before standard treatment. These trials evaluate treatments designed to reduce tumor size to a point where it can be definitively treated by therapies that are considered the best standard treatment. For example, clinical trials have shown that chemotherapy can reduce an inoperable breast cancer to a size that can be removed surgically.

Both adjuvant and neoadjuvant trials are phased like other treatment protocols, with the phase dependent on the major objective of the trial.

#### *Who Participates*

People who have no clinical evidence of disease after primary treatment, but who are at high risk of recurrence, participate in adjuvant trials. People whose cancer, once reduced, could be effectively treated by therapies considered the best standard treatment participate in neoadjuvant trials.

### Prevention Trials

Cancer prevention trials are designed for people at risk of developing cancer. The trials evaluate the safety and effectiveness of various risk reduction strategies. The two types of prevention trials answer the following questions:

- **Action trials:** Can a person's actions—such as exercising more or quitting smoking—prevent cancer?
- **Agent trials:** Can taking certain medicines, vitamins, minerals, or food supplements lower the risk of certain types of cancer? (Agent trials are also known as chemoprevention trials.)

Chemoprevention trials compare a promising new prevention agent or technique with a standard agent or technique, or placebo. The investigational group takes the agent being studied; the control group takes either the standard agent that is being compared to the study agent or—because there may be no standard agent—a look-alike agent that contains no active ingredient, called a placebo.

#### *Who Participates*

Prevention trials seek participants from various age groups and socioeconomic backgrounds or people who have combinations of cancer risk factors. Participants in prevention trials are otherwise healthy individuals who are at risk for cancer.

#### *Possible Benefits*

- If the intervention being studied is found to be effective, participants may be among the first to benefit.

#### *Possible Risks*

- New cancer prevention interventions may have unknown side effects or risks.
- The drug intervention may have worse side effects or be less effective than standard preventive measures.
- Even if a new drug or intervention is effective, it may not work for every participant.

### Screening Trials

Screening trials assess the effectiveness of new means of detecting the earliest stages of cancer. In addition, these trials examine whether early treatment improves overall survival or disease-free survival. Screening tools include imaging tests and laboratory tests.

#### *Who Participates*

Participants are healthy and may be chosen to represent particular age groups or socioeconomic backgrounds. Screening trials also seek participants with certain cancer risk factors, such as belonging to a family that has a genetic predisposition to cancer.

#### *Possible Benefits*

- For many types of cancer, detecting the disease at an early stage can result in earlier treatment and an improved outcome.
- Screening trials often encourage participants to continue screening on a regular basis, which can lead to improved health overall.
- Screening trials for people with a genetic predisposition to cancer can alert other family members to begin regular cancer screening, aid in early detection, and help in the diagnosis and treatment of potential cancers.

#### *Possible Risks*

- Some of the imaging procedures used in screening may be uncomfortable or require participants to be in confined spaces for some period of time.
- If an imaging technique is being studied, participants may be exposed to x-rays or radioactive substances.
- Tests can be time consuming.

### Diagnostic Trials

Diagnostic trials develop better tools for physicians to use in classifying types and phases of cancer, and in managing the care of people with cancer. Some trials compare the ability of two diagnostic techniques to provide information about a suspected cancer. Genetic tests are being evaluated as diagnostic tools to classify cancers further, thus helping physicians direct cancer therapy and improve treatments for people with specific genetic mutations. Diagnostic trials may also evaluate techniques designed to measure and monitor cancer response more accurately or less invasively, such as using a new imaging tool that eliminates the need for surgery.

#### *Who Participates*

Participants include people with cancer or symptoms suggesting cancer.

#### *Possible Benefits*

- The diagnostic test under investigation may be better and less invasive than current tests.
- A new diagnostic tool may help detect cancer recurrence, which could lead to improved outcomes.

#### *Possible Risks*

- Participation in a diagnostic trial may require people to take multiple tests.

### Genetics Trials

Actual genetic intervention (such as gene-transfer) trials are few in number, however trials are underway where actual cellular manipulation at the gene level occurs. Most genetics research involves looking at tissue or blood samples from large populations of people in order to determine how genetic make-up can influence detection, diagnosis, prognosis, and treatment. This genetic epidemiologic research does not involve any actual intervention. Rather, it is designed to broaden understanding of the causes of cancer. Genetics research is also being used to develop targeted treatments based on the genetics of a tumor. Genetics research is a critical component of cancer research

because it helps scientists understand the causes of cancer and can lead to developing clinical trials for the prevention, detection, and treatment of cancer.

### Quality-of-Life and Supportive Care Trials

Quality-of-life and supportive care trials test interventions designed to improve quality of life for people with cancer and their families. They seek better therapies or psychosocial interventions for people experiencing nutrition problems, infection, pain, nausea and vomiting, sleep disorders, depression, and other effects of cancer or its treatment. Some supportive care trials target families and caregivers to help them cope. The effectiveness of supportive care trials may be measured either:

- **Subjectively:** Is the person's pain reduced?
- **Objectively:** Are the white blood cell counts improved?

#### *Who Participates*

Participants include:

- People who are interested in relief from the effects of cancer or its treatment
- Family members or others who want support in caregiving or meeting their own needs

#### *Possible Benefits*

- If the intervention is found to be effective a person with cancer and his or her family may be among the first to benefit.

#### *Possible Risks*

- People may not benefit from participating in the trial.

# Special Access Programs

Investigational drugs may be made available for use outside of a clinical trial. Working with NCI and other sponsors, FDA has established special conditions under which a person with cancer can receive unapproved cancer drugs that have shown clinical benefit.

## Group C

In the 1970s, NCI researchers became concerned about the time it took to bring to market investigational drugs found to have antitumor activity. Working with FDA, NCI established the "Group C" classification to allow access to drugs with reproducible activity. Group C drugs are provided to physicians who register using a special form to ensure that the person they're treating qualifies under guideline protocols for the drug.

Each Group C drug protocol specifies eligibility, reporting methodology, and drug use. Group C designation speeds new drugs to people who need them most. The process allows NCI to gather important information on the safety as well as activity of the drugs in the settings where they will be most used after FDA approval. Drugs are placed in the Group C category by agreement between FDA and NCI. Group C drugs are always provided free of charge, and the Centers for Medicare and Medicaid Services (formerly the Health Care Financing Administration) provides coverage for its beneficiaries for care associated with Group C therapy.

## Treatment IND

In 1987, FDA began authorizing the use of new drugs still in the development process to treat certain seriously ill people. In these cases, the process is referred to as a treatment Investigational New Drug (IND) application. Clinical trials of the new drug must already be underway and have demonstrated positive results.

FDA sets guidelines about:

- What serious and life-threatening illnesses constitute
- How much must be known about a drug's side effects and benefits
- Where physicians can obtain the drug for treatment

For many seriously ill people, the possible benefits outweigh the risks associated with taking an unapproved drug.

Less common ways that people can receive investigational drugs are through expanded access protocols or mechanisms known as special or compassionate exception.

## Expanded Access Protocols

Expanded access protocols are available for a limited number of well-studied investigational drugs awaiting final FDA approval. Expanded access allows a wider group of people to be treated with a drug. The purpose is to make investigational drugs that have significant activity against specific cancers available before the FDA approval process has been completed.

The IND sponsor must apply to FDA to make the drug available through an expanded access protocol. There must be enough evidence from completed trials to show that the drug may be effective to treat a specific type of cancer and that it does not have unreasonable risks. FDA generally approves expanded access only if no other satisfactory treatments are available for the disease.

## Special or Compassionate Exception

People who do not meet the eligibility criteria for a clinical trial of an investigational drug may be eligible to receive the drug. The person's doctor contacts the trial sponsor and provides the person's medical information and treatment history; requests are evaluated on a case-by-case basis. FDA must approve each request to provide the drug outside a clinical trial. There should be reasonable expectation that the drug will prolong survival or improve quality of life.

Considerations when determining whether a person may receive an investigational drug as a special exception include:

- Is the person ineligible for a clinical trial?
- Have standard therapies been exhausted?
- Is there objective evidence that the investigational agent is effective for the person's type of disease?
- Can the drug potentially benefit the person?
- What is the risk to the person?

In some cases, even people who qualify might not be able to obtain the drug if it is in limited quantity and high demand.